

TABLE 1: Patient characteristics at study entry.

| Characteristics | AHOD, <i>n</i> = 794 <i>n</i> (%) | TAHOD, <i>n</i> = 2053 <i>n</i> (%) | <i>P</i> * |
|--------------------------------------|---|---|------------|
| Age (years) | | | |
| Mean ± SD | 45 (±9.8) | 38.6 (±10) | <0.001 |
| Gender | | | |
| Male | 761 (96) | 1,484 (72.2) | <0.001 |
| Female | 30 (3.8) | 567 (27.6) | |
| Transgender*** | 03 (0.4) | 02 (0.1) | |
| HIV exposure category | | | |
| Homosexual contact ± IDU | 618 (78.4) | 485 (23.7) | <0.001 |
| IDU ± heterosexual | 25 (3.2) | 45 (2.2) | |
| Heterosexual | 65 (8.2) | 1,341 (65.6) | |
| Other | 80 (10.2) | 174 (8.5) | |
| Missing | 06 (0.7) | 08 (0.4) | |
| HBV coinfection | | | |
| Negative | 649 (81.8) | 1,376 (67) | <0.001 |
| Positive | 22 (2.8) | 171 (8.3) | |
| Missing/never tested | 123 (15.5) | 506 (24.6) | |
| HCV coinfection | | | |
| Negative | 631 (79.5) | 1,365 (66.5) | <0.001 |
| Positive | 87 (11) | 128 (6.2) | |
| Missing/never tested | 76 (10) | 560 (27.3) | |
| HIV RNA < 500 copies/mL | | | |
| Missing | 58 (7.3) | 880 (43) | <0.001 |
| CD4+ count cells/μL | 360 (219–569) | 161 (50–280) | <0.001** |
| Median (IQR) | | | |
| Missing | 58 (7.3) | 264 (12.9) | |
| Cumulative exposure to cART in years | | | |
| Median (IQR) | 2 (0–8.2) | 0 (0–0.2) | <0.001** |
| Number ART naive | 320 (40.3) | 1460 (71) | |
| Body mass index (kg/m ²) | | | |
| Mean (±SD) | 24 (±3.4) | 21 (±3.4) | <0.001 |
| Missing | 528 (66.5) | 1016 (49.5) | |
| Total cholesterol mmol/L | | | |
| Mean (±SD) | 5.15 (±1.3) | 4.88 (±1.4) | <0.001 |
| Triglycerides mmol/L | | | |
| Mean (±SD) | 2.44 (±2) | 2.40 (±2.3) | 0.678 |
| HDL-C mmol/L | | | |
| Mean (±SD) | 1.15 (±0.5) | 1.25 (±0.4) | <0.001 |

* Comparison by *t*-test for continuous variables and the χ^2 test for noncontinuous variables. ** Comparison by Wilcoxon rank-sum test. A: AHOD: Australian HIV Observational Database; T: TAHOD: TREAT Asia HIV Observational Database. cART: combinational antiretroviral therapy; HBV: hepatitis B coinfection; HCV: hepatitis C coinfection; IDU: Intravenous drug user; IQR: interquartile range; SD: standard deviation. *** Transgender participants were classified as males in the multivariable analyses.

4. Discussion

In this study, we examined the mean differences in lipids between various cART regimens in TAHOD and AHOD cohorts. We found that the relationship between regimen and lipids differed by cohort only in the analysis of total cholesterol level. For total cholesterol, the magnitude of effect of regimen differed between cohorts such that TAHOD participants tended to have slightly lower total cholesterol for most regimens (most notably for the NRTIs (+TDF) + PI (+ATV) and the NRTIs + PI regimens). Overall, we found that the NRTIs (+TDF) + NVP and the NRTIs (+TDF) + PI (+ATV) regimens were associated with the most favorable lipid profile, whereas the NRTIs + PI and the NRTIs + EFV regimens were associated with the least favorable lipid profiles.

These regimen/lipid association findings are consistent with the literature from Western countries [5–8, 17]. The few studies that have reported lipid results from Asian population also suggest an adverse impact of PI-based and EFV-based regimens on lipids as compared to non-PI-based and NVP-based regimens, respectively [18, 19]. However, these studies were performed in clinical-trial populations, and in one study [19], NVP was given at 400 mg once a day, instead of the recommended 200 mg twice a day dosing schedule. Also, they did not report usage of TDF- or ATV-based regimens.

The observed differences in mean total cholesterol between TAHOD and AHOD cohorts, though statistically significant, were of small magnitude. The differences could be due to variations in race/ethnicity or dietary, environmental, and lifestyle factors [20]. The clinical relevance of these differences, particularly the impact of these differences on overall risk of CHD, is uncertain. In our study, TAHOD participants had average total cholesterol up to 0.5 mmol/L lower than AHOD for the NRTIs + PI regimen (Figure 1(a)). Studies on treated HIV-infected populations have suggested that a difference of 1 mmol/L in total cholesterol may be associated with difference of about 25% in risk of CHD [21, 22]. Further, TAHOD participants, for any given regimen, had higher triglycerides which have been associated with greater risk of CHD [23]. The CHD events in cART-treated HIV patients are thought to be multifactorial in origin, with a possible role of dyslipidemia, cART, HIV-associated inflammatory process, and traditional risk factors [1, 21]. We did not have data on other CHD risk factors, with which we could calculate the overall Framingham risk score for each cohort. Future studies should therefore evaluate their impact on risk of CHD events in treated HIV populations in Asia.

There are further limitations to this study. We divided each class of ART according to those shown to have favorable impact on lipids, that is, TDF, ATV, and NVP [5, 7, 8]. However, such a classification did not allow us to examine the impact of other individual drugs in each class. Further, we did not have information on use of lipid-lowering medications, which are likely to differ between TAHOD and AHOD. It is likely that since TAHOD participants were younger and mostly from low-middle income countries, they may have a lower rate of use of lipid-lowering medications, as compared to those in AHOD.

TABLE 2: Number and frequency of total cholesterol measurements by type of regimen and cohort.

| cART Regimen | AHOD No. of patients* | AHOD median (range) no. of measurements per patient | AHOD no. (%) of measurements | TAHOD no. of patients* | TAHOD median (range) no. of measurements per patient | TAHOD no. (%) of measurements |
|--------------------------|-----------------------|---|------------------------------|------------------------|--|-------------------------------|
| NRTIs (+TDF) + NVP | 122 | 2 (1–6) | 247 (10.8) | 70 | 1 (1–4) | 108 (1.9) |
| NRTIs (+TDF) + EFV | 131 | 2 (1–4) | 245 (10.7) | 90 | 1 (1–4) | 147 (2.6) |
| NRTIs + NVP | 155 | 2 (1–6) | 342 (14.9) | 696 | 1 (1–8) | 1157 (20.6) |
| NRTIs + EFV | 97 | 2 (1–4) | 211 (9.2) | 684 | 2 (1–10) | 1487 (26.5) |
| NRTIs (+TDF) + PI (+ATV) | 140 | 1 (1–5) | 266 (11.6) | 20 | 1 (1–4) | 28 (0.5) |
| NRTIs (+TDF) + PI | 187 | 2 (1–7) | 410 (17.9) | 137 | 3 (1–6) | 367 (6.5) |
| NRTIs + PI (+ATV) | 78 | 2 (1–5) | 178 (7.7) | 232 | 3 (1–6) | 610 (10.9) |
| NRTIs + PI | 184 | 2 (1–6) | 396 (17.2) | 620 | 3 (1–12) | 1698 (30.3) |
| Total | 1094 | | 2295 (100) | 2548 | | 5602 (100) |

* Each patient could contribute to more than one regimen. AHOD: Australian HIV Observational Database; ATV: Atazanavir; EFV: Efavirenz; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTIs: nucleoside reverse transcriptase inhibitors; NVP: nevirapine; PI: protease inhibitor; TAHOD: TREAT Asia HIV Observational Database; TDF: tenofovir. Key. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

TABLE 3: Adjusted analyses for triglycerides, HDL-C, and total cholesterol : HDL-C ratio.**

| Covariate | Mean difference in triglycerides mmol/L (95% CI) | Mean difference in HDL-C mmol/L (95% CI) | Mean difference in total cholesterol : HDL-C ratio (95% CI) |
|-------------------------|--|--|---|
| Regimen | | | |
| NRTIs (+TDF) + NVP | Reference | Reference | Reference |
| NRTIs (+TDF) + EFV | 0.17 (–0.19 to 0.53) | 0.01 (–0.06 to 0.08) | 0.16 (–0.16 to 0.47) |
| NRTIs + NVP | 0.58 (0.29 to 0.87) | 0.15 (0.08 to 0.21) | 0.13 (–0.12 to 0.39) |
| NRTIs + EFV | 0.64 (0.34 to 0.95) | 0.09 (0.03 to 0.16) | 0.29 (0.01 to 0.56) |
| NRTIs (+TDF) + PI(+ATV) | 0.15 (–0.22 to 0.52) | –0.03 (–0.11 to 0.05) | 0.29 (–0.04 to 0.62) |
| NRTIs (+TDF) + PI | 1.06 (0.73 to 1.38) | –0.02 (–0.09 to 0.05) | 0.66 (0.37 to 0.95) |
| NRTIs + PI(+ATV) | 0.57 (0.24 to 0.90) | 0.03 (–0.05 to 0.10) | 0.34 (0.02 to 0.65) |
| NRTIs + PI | 1.13 (0.83 to 1.43) | 0.01 (–0.06 to 0.07) | 0.75 (0.47 to 1.03) |
| <i>P</i> | <0.001 | <0.001 | <0.001 |
| Cohort | | | |
| AHOD | Reference | Reference | Reference |
| TAHOD | 0.33 (0.11 to 0.55) | 0.04 (–0.01 to 0.09) | –0.16 (–0.40 to 0.08) |
| <i>P</i> | 0.003 | 0.146 | 0.187 |

Table shows independent effects of regimen and cohort variables in adjusted analyses. Since the interaction term between these variables was not significant, it was not included in the models. Figure 1 shows the interaction between regimen and cohort variables.

**Multivariable models were *a priori* adjusted for time on given regimen, Hepatitis B and/or C coinfections, age, gender, HIV RNA viral load copies/mL, CD4+ T-cell count, BMI, cumulative exposure to cART at the start of regimen, and HIV exposure category. AHOD: Australian HIV Observational Database, ATV: Atazanavir; cART: combination antiretroviral therapy; CI: confidence interval; EFV: Efavirenz; HBV: Hepatitis B co-infection; HCV: Hepatitis C co-infection; IDU: Intravenous drug user; NNRTI: nonnucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors, NVP: nevirapine, PI: protease inhibitor, TAHOD: TREAT Asia HIV Observational Database; TDF: Tenofovir. Key. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

However, TAHOD participants had lower total cholesterol for most regimens than those in AHOD, suggesting residual confounding, racial differences, or possibly higher use of lipid lowering medications. Also, lipid values were measured in site-specific laboratories which may introduce variation in results. However, such a variation is unlikely to result in any systematic differences in total cholesterol that we observed. Furthermore, patients in AHOD tended to be more treatment-experienced than TAHOD; however, adjusting

for cumulative cART exposure did not change our results. Nevertheless, any residual confounding from these and other unmeasured factors cannot be ruled out. Lastly, we did not have pre-cART lipid data to compare with post-cART data in each cohort, which would have provided clearer comparisons of change in lipids in response to cART between the cohorts. Keeping these limitations in mind, our results were however robust when restricted to those (i) documented to be taken after over-night fasting, (ii) with documented race/ethnicity,

and (iii) adjusting for differential use of d4t, suggesting that these factors were unlikely to impact our results.

Strengths of our study include TAHOD and AHOD being founded on similar methodology thereby reducing the likelihood of confounding due to methodological differences. Also, the large sample size available allowed us to analyse several regimens, including those with TDF and ATV, which are less frequently used in low-middle income countries [10]. Moreover, availability of lipid measurements on several time-points on each regimen allowed us to adjust for time spent on each regimen of interest.

In summary, our findings suggest that the impact of various ART regimens on lipids is largely similar in TAHOD and AHOD cohorts and that the newer drugs such as TDF and ATV are likely to provide similar benefit in terms of lipid profiles in both populations. We also found that TAHOD participants may have slightly lower mean total cholesterol for most regimens, although the clinical significance of this difference is uncertain. These findings contribute to the gap in evidence from Asian settings. Future studies should report pre- to post-ART monitoring of lipids and information on Framingham risk score in diverse populations.

Funding

The TREAT Asia HIV Observational Database and the Australian HIV Observational Database are part of the Asia Pacific HIV Observational Database and are initiatives of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the following institutes of the U.S. National Institutes of Health (NIH): National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), the Office of the Director (OD), and the National Cancer Institute (NCI), as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (Grant no. U01AI069907). Additional support is provided by the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds. The Kirby Institute for Infection and Immunity in society is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

The writing committee would like to acknowledge several thousands of patients, the *TAHOD Steering Committee* (C. V. Mean, V. Saphonn*, and K. Vohith, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; F. J. Zhang*, H. X. Zhao, and N. Han, Beijing Ditan Hospital, Capital Medical University, Beijing, China; P. C. K. Li*, and

M. P. Lee, Queen Elizabeth Hospital, Hong Kong, China; N. Kumarasamy*, S. Saghayam, and C. Ezhilarasi, YRG Centre for AIDS Research and Education, Chennai, India; S. Pujari*[†], K. Joshi, and A. Makane, Institute of Infectious Diseases, Pune, India; T. P. Merati*, D. N. Wirawan and F. Yuliana, Faculty of Medicine Udayana University and Sanglah Hospital, Bali, Indonesia; E. Yuniastuti*, Working Group on AIDS Faculty of Medicine, University of Indonesia/Ciptomangunkusumo Hospital, Jakarta, Indonesia; S. Oka*, J. Tanuma, and M. Honda, National Center for Global Health and Medicine, Tokyo, Japan; J. Y. Choi*, S. H. Han, and J. M. Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; C. K. C. Lee*, B. L. H. Sim, and R. David, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A. Kamarulzaman*[‡] and A. Kajindran, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; R. Ditango*, E. Uy, and R. Bantique, Research Institute for Tropical Medicine, Manila, Philippines; Y. M. A. Chen*, W. W. Wong, and L. H. Kuo, Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan; O. T. Ng*, P. L. Lim, A. Chua, and A. Loh, Tan Tock Seng Hospital, Singapore; P. Phanuphak*, K. Ruxrungtham and M. Khongphattananayothin, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S. Kiertiburanakul*, S. Sungkanuparph, and N. Sanmeema, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; T. Sirisanthana*, R. Chaiwarith and W. Kotarathititum, Research Institute for Health Sciences, Chiang Mai, Thailand; V. K. Nguyen*, V. H. Bui and T. T. Cao, National Hospital for Tropical Diseases, Hanoi, Vietnam; T. T. Pham*, D. D. Cuong, and H. L. Ha, Bach Mai Hospital, Hanoi, Vietnam; A. H. Sohn*, N. Durier* and B. Petersen, TREAT Asia, amfAR—The Foundation for AIDS Research, Bangkok, Thailand; D.A. Cooper, M. G. Law*, J. Zhou*, and A. Jiamsakul, The Kirby Institute, The University of New South Wales, Sydney, Australia. (*TAHOD Steering Committee member; [†]Steering Committee Chair; [‡]Co-Chair.) and the *AHOD Steering Committee* (The Australian HIV Observational Database: D. Ellis, General Medical Practice, Coffs Harbour, NSW; J. Chuah*, M. Ngieng, B. Dickson, Gold Coast Sexual Health Clinic, Miami, QLD; M Bloch, T. Franic, S. Agrawal, and N. Cunningham, Holdsworth House General Practice, Darlinghurst, NSW; R. Moore, S. Edwards, and P. Locke, Northside Clinic, North Fitzroy, VIC; D. Nolan, C. Forsdyke, and J. Skett, Department of Clinical Immunology, Royal Perth Hospital, Perth, WA; N. J. Roth*[†], J. Nicolson, Prahran Market Clinic, South Yarra, VIC; D. Allen, P. Maudlin Holden Street Clinic, Gosford, NSW; D. Smith, C. Mincham, and C. Gray, Lismore Sexual Health and AIDS Services, Lismore, NSW; D. Baker* and R. Vale, East Sydney Doctors, Darlinghurst, NSW; D. Russell and S. Downing, Cairns Sexual Health Service, Cairns, QLD; D. Templeton, C O'Connor, Royal Prince Alfred Hospital Sexual Health, Camperdown, NSW; D. Sowden and K McGill, Clinic 87, Sunshine Coast and Cooloola HIV Sexual Health Service, Nambour, QLD; D. Orth and D. Youds, Gladstone Road Medical Centre, Highgate Hill,

QLD; E. Jackson, Blue Mountains Sexual Health and HIV Clinic, Katoomba, NSW; T. Read and J. Silvers, Melbourne Sexual Health Centre, Melbourne, VIC; A. Kulatunga, P. Knibbs and Communicable Disease Centre, Royal Darwin Hospital, Darwin, NT; J. Hoy, K. Watson*, M. Bryant, S. Price, The Alfred Hospital, Melbourne, VIC; M. Gotowski, S. Taylor and L. Stuart-Hill, Tamworth Sexual Health Service, Tamworth, NSW; D. Cooper, A. Carr, K. Hesse and R. Norris St Vincent's Hospital, Darlinghurst, NSW; R. Finlayson and I. Prone, Taylor Square Private Clinic, Darlinghurst, NSW; M. T. Liang, Nepean Sexual Health and HIV Clinic, Penrith, NSW; M. Kelly, A. Gibson and H. Magon, AIDS Medical Unit, Brisbane, QLD; K. Brown, N. Skobalj, Illawarra Sexual Health Clinic, Warrawong, NSW; L. Wray and H. Lu, Sydney Sexual Health Centre, Sydney, NSW; W. Donohue, The Care and Prevention Programme, Adelaide University, Adelaide, SA; I. Woolley, M. Giles, and T. Korman, Monash Medical Centre, Clayton, VIC; Dubbo Sexual Health Centre, Dubbo, NSW; P. Canavan*, National Association of People Living with HIV/AIDS; C. Lawrence*, National Aboriginal Community Controlled Health Organisation; B. Mulhall*, School of Public Health, University of Sydney, Sydney, NSW; M. Law*, K. Petoumenos*, and S. Marashi Pour*, Courtney Bendall*, National Centre in HIV Epidemiology and Clinical Research, University of NSW, Sydney; NSW; (*Steering Committee member 2010; †Current Steering Committee chair). The authors acknowledge the Cause of Death (CoDE) reviewers AHOD reviewers: D. Sowden, D. Templeton, A. Carr, J. Hoy, L. Wray, J. Chuah, K. Morwood, T. Read, N. Roth, I. Woolley, M. Kelly, J. Broom). The authors also thank Mr. Hamish McManus and Mr. Stephen Wright for help with STATA programming.

References

- [1] C. J. Fichtenbaum, "Metabolic abnormalities associated with HIV infection and antiretroviral therapy," *Current Infectious Disease Reports*, vol. 11, no. 1, pp. 84–92, 2009.
- [2] E. Fontas, F. Van Leth, C. A. Sabin et al., "Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles?" *Journal of Infectious Diseases*, vol. 189, no. 6, pp. 1056–1074, 2004.
- [3] P. W. G. Mallon, "Antiretroviral therapy-induced lipid alterations: in-vitro, animal and human studies," *Current Opinion in HIV and AIDS*, vol. 2, no. 4, pp. 282–292, 2007.
- [4] S. A. Riddler, X. Li, H. Chu et al., "Longitudinal changes in serum lipids among HIV-infected men on highly active antiretroviral therapy," *HIV Medicine*, vol. 8, no. 5, pp. 280–287, 2007.
- [5] A. Hill, W. Sawyer, and B. Gazzard, "Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels," *HIV Clinical Trials*, vol. 10, no. 1, pp. 1–12, 2009.
- [6] F. Van Leth, P. Phanuphak, E. Stroes et al., "Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naïve patients infected with HIV-1," *Plos Medicine*, vol. 1, no. 1, article no. e19, pp. 064–074, 2004.
- [7] D. Carey, J. Amin, M. Boyd, K. Petoumenos, and S. Emery, "Lipid profiles in HIV-infected adults receiving atazanavir and atazanavir/ritonavir: systematic review and meta-analysis of randomized controlled trials," *Journal of Antimicrobial Chemotherapy*, vol. 65, no. 9, Article ID dkq231, pp. 1878–1888, 2010.
- [8] H. M. Crane, C. Grunfeld, J. H. Willig et al., "Impact of nrtis on lipid levels among a large HIV-infected cohort initiating antiretroviral therapy in clinical care," *AIDS*, vol. 25, no. 2, pp. 185–195, 2011.
- [9] World Health Organisation, "Transaction prices for Antiretroviral Medicines and HIV Diagnostics from 2008 to March 2010," 2010.
- [10] World Health Organisation, "Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: a Public Health Approach," 2007.
- [11] A. S. Foulkes, D. A. Wohl, I. Frank et al., "Associations among race/ethnicity, apoc-iii genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy," *Plos Medicine*, vol. 3, no. 3, e52, pp. 337–347, 2006.
- [12] M. J. Míguez-Burbano, J. E. Lewis, and R. Malow, "Alcohol and race/ethnicity elicit different changes in lipid profiles in HIV-infected individuals receiving highly active antiretroviral therapy," *Journal of the Association of Nurses in AIDS Care*, vol. 20, no. 3, pp. 176–183, 2009.
- [13] R. J. Shephard, M. Cox, and C. West, "Some factors influencing serum lipid levels in a working population," *Atherosclerosis*, vol. 35, no. 3, pp. 287–300, 1980.
- [14] A. C. Achhra, J. Zhou, J. Y. Choi et al., "The clinical significance of cd4 counts in asian and caucasian HIV-infected populations: results from tahod and ahod," *Journal of the International Association of Physicians in AIDS Care*, vol. 10, no. 3, pp. 160–170, 2011.
- [15] Australian HIV Observational Database, "Rates of combination antiretroviral treatment change in Australia," *HIV Medicine*, vol. 3, pp. 28–36, 2002.
- [16] J. Zhou, N. Kumarasamy, R. Ditangco et al., "The treat asia HIV observational database: baseline and retrospective data," *Journal of Acquired Immune Deficiency Syndromes*, vol. 38, no. 2, pp. 174–179, 2005.
- [17] "1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults," *MMWR Recommendations and Reports*, vol. 41, pp. 1–19, 1992.
- [18] S. J. Kerr, C. Duncombe, A. Avihingsanon et al., "Dyslipidemia in an asian population after treatment for two years with protease inhibitor-containing regimens," *Journal of the International Association of Physicians in AIDS Care*, vol. 6, no. 1, pp. 36–46, 2007.
- [19] C. Padmapriyadarsini, S. R. Kumar, N. Terrin et al., "Dyslipidemia among HIV-infected patients with tuberculosis taking once-daily nonnucleoside reverse-transcriptase inhibitor-based antiretroviral therapy in india," *Clinical Infectious Diseases*, vol. 52, no. 4, pp. 540–546, 2011.
- [20] A. Morris and K. C. Ferdinand, "Hyperlipidemia in racial/ethnic minorities: differences in lipid profiles and the impact of statin therapy," *Clinical Lipidology*, vol. 4, no. 6, pp. 741–754, 2009.
- [21] N. Friis-Moller, R. Thiebaut, P. Reiss et al., "Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study," *European Journal of Cardiovascular Prevention & Rehabilitation*, vol. 17, pp. 491–501, 2010.
- [22] M. Schambelan, P. W. F. Wilson, K. E. Yarasheski et al., "Development of appropriate coronary heart disease risk

prediction models in HIV-infected patients,” *Circulation*, vol. 118, no. 2, pp. e48–e53, 2008.

- [23] S. W. Worm, D. A. Kamara, P. Reiss et al., “Elevated triglycerides and risk of myocardial infarction in HIV-positive persons,” *AIDS*, vol. 25, no. 12, pp. 1497–1504, 2011.

Clinical Study

Loss to Followup in HIV-Infected Patients from Asia-Pacific Region: Results from TAHOD

Jialun Zhou,¹ Junko Tanuma,² Romanee Chaiwarith,³ Christopher K. C. Lee,⁴ Matthew G. Law,¹ Nagalingeswaran Kumarasamy,⁵ Praphan Phanuphak,⁶ Yi-Ming A. Chen,⁷ Sasisopin Kiertiburanakul,⁸ Fujie Zhang,⁹ Saphonn Vonthanak,¹⁰ Rossana Ditangco,¹¹ Sanjay Pujari,¹² Jun Yong Choi,¹³ Tuti Parwati Merati,¹⁴ Evy Yuniastuti,¹⁵ Patrick C. K. Li,¹⁶ Adeeba Kamarulzaman,¹⁷ Van Kinh Nguyen,¹⁸ Thi Thanh Thuy Pham,¹⁹ and Poh Lian Lim²⁰

¹ The Kirby Institute, The University of New South Wales, Sydney, NSW 2034, Australia

² National Center for Global Health and Medicine, Tokyo 162-8655, Japan

³ Research Institute for Health Sciences, Chiang Mai 50200, Thailand

⁴ Department of Medicine, Hospital Sungai Buloh, 47000 Kuala Lumpur, Malaysia

⁵ YRG Centre for AIDS Research and Education, Chennai 600113, India

⁶ HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok 10330, Thailand

⁷ Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei 112, Taiwan

⁸ Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok 10400, Thailand

⁹ Beijing Ditan Hospital, Capital Medical University, Beijing 100050, China

¹⁰ National Center for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia

¹¹ Research Institute for Tropical Medicine, 1781 Manila, Philippines

¹² Institute of Infectious Diseases, Pune 411037, India

¹³ Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul 120-752, Republic of Korea

¹⁴ Faculty of Medicine, Udayana University and Sanglah Hospital, Bali 80233, Indonesia

¹⁵ Working Group on AIDS, Faculty of Medicine, University of Indonesia/Ciptomangunkusumo Hospital, Jakarta 10430, Indonesia

¹⁶ Department of Medicine, Queen Elizabeth Hospital, Hong Kong

¹⁷ Faculty of Medicine, University of Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia

¹⁸ National Hospital for Tropical Diseases, Hanoi, Vietnam

¹⁹ Department of Infectious Diseases, Bach Mai Hospital, Hanoi, Vietnam

²⁰ Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore 308433

Correspondence should be addressed to
Matthew G. Law, mlaw@kirby.unsw.edu.au

Received 26 October 2011; Accepted 14 December 2011

Academic Editor: Anthony Harries

Copyright © 2012 Jialun Zhou et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This study examined characteristics of HIV-infected patients in the TREAT Asia HIV Observational Database who were lost to follow-up (LTFU) from treatment and care. Time from last clinic visit to 31 March 2009 was analysed to determine the interval that best classified LTFU. Patients defined as LTFU were then categorised into permanently LTFU (never returned) and temporary LTFU (re-entered later), and these groups compared. A total of 3626 patients were included (71% male). No clinic visits for 180 days was the best-performing LTFU definition (sensitivity 90.6%, specificity 92.3%). During 7697 person-years of follow-up, 1648 episodes of LTFU were recorded (21.4 per 100-person-years). Patients LTFU were younger ($P = 0.002$), had HIV viral load ≥ 500 copies/mL or missing ($P = 0.021$), had shorter history of HIV infection ($P = 0.048$), and received no, single- or double-antiretroviral therapy, or a triple-drug regimen containing a protease inhibitor ($P < 0.001$). 48% of patients LTFU never returned. These patients were more likely to have low or missing haemoglobin ($P < 0.001$), missing recent HIV viral load ($P < 0.001$), negative hepatitis C test ($P = 0.025$), and previous temporary LTFU episodes ($P < 0.001$). Our analyses suggest that patients not seen at a clinic for 180 days are at high risk of permanent LTFU, and should be aggressively traced.

1. Introduction

Loss to followup (LTFU) in patients receiving antiretroviral therapy can cause serious consequences such as discontinuation of treatment and increased risk of death [1–3]. At a program level, LTFU can make it difficult to evaluate outcomes of treatment and care [4, 5]. In resource-limited settings, where treatment has become rapidly available following the rollout of antiretroviral therapy, LTFU presents even more challenging obstacles that require special consideration and approaches [6, 7].

One of the key questions in patient followup is how to define a patient as LTFU. This has varied in studies conducted in different settings [8–10]. Defining LTFU using a very early threshold, for example, a patient with no clinic visit in the last three months, may result in many patients being considered as LTFU who would return to clinic naturally at a later date. Defining LTFU with a long threshold, for example, one year, may mean delaying too long before any effort is made to track patients potentially at risk of LTFU.

The majority of research into LTFU in HIV-infected patients receiving antiretroviral treatment in resource-limited settings has been conducted in the sub-Saharan Africa region [3, 10–13]. A few studies have been conducted among Asian, mostly female, patients [14–16]. Using data from the TREAT Asia HIV Observational Database (TAHOD), this study was carried out to find the best-performing definition of LTFU and examine the characteristics of HIV-infected patients from the Asia-Pacific who were LTFU from treatment and care.

2. Methods

Established in 2003, TAHOD is a collaborative observational cohort study involving 18 sites in the Asia-Pacific region (see Acknowledgement). Detailed methods have been published previously [17]. Briefly, each site recruited approximately 200–300 HIV-infected patients, with recruitment based on a consecutive series of patients regularly attending a given site from a particular start-up time. Ethical approval for the study was obtained from the University of New South Wales Ethics Committee, Western Institutional Review Board, and respective local ethics committee from each TAHOD participating site.

The following data were collected: patient demographics and baseline data, CD4 and CD8 count, HIV viral load, prior and new AIDS defining illness (ADI), date and cause of death, prior and current prescribed antiretroviral treatment (ART), and reason for treatment change. Data were collected according to a common protocol. Upon recruitment, all available data prior to entry to TAHOD (considered as retrospective data) were extracted from patient case notes. Prospective data were updated six-monthly at each clinic and transferred to the data management centre for aggregation and analyses in March and September each year. TAHOD sites were encouraged to contact patients who have not been seen in the clinics in the previous 12 months.

TAHOD data submitted at March 2009 and March 2010 were used to find the best-performing definition of LTFU.

TAHOD patients who had no followup after recruitment were not included in this analysis. Patients who were not seen in clinic for more than 12 months prior to the March 2010 data submission (i.e., last clinic visit prior to March 2009) were considered to be truly LTFU. The days between the last clinical visit and 31 March 2009 in the March 2009 data transfer were then used to find the interval that best classified a true LTFU in the following way. A series of cutoffs were considered, from ten to 365 days, to define patients as potentially LTFU. Each of these definitions of potential LTFU was compared with the gold standard of true LTFU, defined as no patient followup in the 12 months prior to 31 March 2010. The sensitivity and specificity of each cutoff in identifying true LTFU were calculated, and the best performing cutoff identified using the area under the receiver operator characteristic (ROC) curve. The optimal definition of LTFU identified in terms of maximising the sensitivity and specificity of true LTFU was found to be 180 days (see Results). This definition was then used in the risk factor analyses that follow.

Followup started from the last clinic visit at the March 2007 data submission. Patients who were considered LTFU before March 2007 (i.e., had no clinic visits 180 days before 31 March 2007) were excluded from the analysis. For patients enrolled after March 2007, the followup started at the time of enrolment. In terms of calculating person-years of followup, the end of followup for patients who had no clinic visit for 180 days and so were considered as LTFU was defined as 90 days after their last clinic visit. For patients not considered LTFU, the end of followup was also defined as 90 days after their last clinic visit. If a patient died, the followup was censored on the date of death if the date was within 180 days of their last clinic visit. Patients who died after March 2007 were considered to have complete followup. It should be noted that patients who were considered LTFU could return to clinic and reenter followup. The start of this reentry to followup was defined as 3 months prior to the first clinic visit that reinitiated followup. The patients that reentered followup could also be re-LTFU if the patient subsequently did not attend clinic for more than 180 days. The definitions we adopted were consistent with those in a previous study [18].

The rates of LTFU were calculated by the number of total LTFU periods divided by the total duration of followup contributed by the patients included in the analysis [18]. Because of the reentering and re-LTFU, patients could contribute more than one episode of LTFU in this analysis. The rates were further calculated in different strata, including age, sex, exposure category, hepatitis B and C infection, year since HIV infection, calendar year, the latest CD4 count and viral load, antiretroviral treatment status, CDC disease stages, prophylaxis (coded as receiving or not), and haemoglobin level, all taken at the start of each episode.

Factors associated with LTFU were assessed by multivariate Poisson regression models, using generalised estimating equations, to allow for multiple events of LTFU in the same patients. CD4 count, HIV viral load, antiretroviral treatment, AIDS diagnosis, and haemoglobin tests were included as

TABLE 1: Receiver operating characteristic (ROC) analysis for the best-performing definition for loss to followup.

| Cutoff (days) | Sensitivity (%) | Specificity (%) | Area under ROC | Cutoff (days) | Sensitivity (%) | Specificity (%) | Area under ROC |
|---------------|-----------------|-----------------|----------------|---------------|-----------------|-----------------|----------------|
| 10 | 99.67 | 16.97 | 58.32 | 160 | 90.96 | 90.77 | 90.87 |
| 20 | 99.02 | 24.32 | 61.67 | 170 | 90.64 | 91.44 | 91.04 |
| 30 | 98.05 | 31.31 | 64.68 | 175 | 90.64 | 92.05 | 91.34 |
| 40 | 96.82 | 39.90 | 68.36 | 180 | 90.55 | 92.26 | 91.41 |
| 50 | 96.34 | 49.52 | 72.93 | 185 | 90.23 | 92.53 | 91.38 |
| 60 | 95.77 | 57.20 | 76.48 | 190 | 89.33 | 93.01 | 91.17 |
| 70 | 95.28 | 65.52 | 80.40 | 200 | 88.52 | 93.44 | 90.98 |
| 80 | 95.11 | 71.26 | 83.19 | 210 | 87.79 | 94.13 | 90.96 |
| 90 | 94.71 | 77.62 | 86.16 | 240 | 85.26 | 95.25 | 90.26 |
| 100 | 94.22 | 80.91 | 87.57 | 270 | 83.55 | 96.43 | 89.99 |
| 120 | 93.24 | 86.18 | 89.71 | 300 | 82.00 | 97.04 | 89.52 |
| 150 | 91.53 | 90.17 | 90.85 | 365 | 78.99 | 97.73 | 88.36 |

True LTFU defined as no patient followup in the 12 month prior to 31 March 2010. Each cutoff used as a potential definition of LTFU was the days between last clinical visit and 31 March 2009 in the March 2009 data transfer. The sensitivity and specificity of each cutoff in identifying true LTFU were calculated, and the optimal cutoff identified based on ROC analysis.

time-dependent variables and updated at the time the new measurement or diagnosis was available.

Patients who had at least one episode of LTFU were then categorised into two groups: those who had no more clinical visits in the database (permanently LTFU) and those who later reentered followup (temporary LTFU). Multivariate logistic regression models were used to compare the characteristics in patients who were considered permanently LTFU with those who were temporary LTFU. All covariates were taken at the end of the episode in patients with truly LTFU or at the end of the first episode in patients considered temporary LTFU.

Multivariate models were built using a forward-stepwise approach. The final model included covariates that remained significant at the $P < 0.05$ level. Nonsignificant variables were also presented and adjusted for the final multivariate models. Data management and statistical analyses were performed using SAS for Windows (SAS Institute Inc., Cary, NC, USA) and Stata (StataCorp, STATA 10.1 for Windows, College Station, TX, USA).

3. Results

In March 2007, there were 2565 patients in the database. 1061 patients were subsequently enrolled in TAHOD up to March 2010. A total of 3626 patients from TAHOD who had follow-up visits in the clinic were included in this analysis. During the study period (from March 2007 to March 2010), there were 54 patients who died and considered to have complete followup.

Using days between last clinic visit and 31 March 2009 in the March 2009 data transfer, we identified the interval that best classifies a true LTFU (i.e., no clinic visit after 31 March 2009). An interval of 180 days was determined as the best-performing definition (Table 1, sensitivity 90.6%, specificity 92.3%). Using 180 days as the LTFU cutoff, during 7697 person-years of followup, a total of 1648 episodes of LTFU

from 1298 patients were identified, giving a crude LTFU rate of 21.4 per 100 person-years (95% confidence interval, CI, 20.4 to 22.5). Of those 1648 episodes of LTFU identified using 180 days as the cutoff, 48% were considered permanently LTFU (i.e., the patient did not return to clinic before 31 March 2010), corresponding to 45% of the 1298 patients.

The patient characteristics are summarised in Table 2. The majority of patients were male (71%), aged between 36 and 45 years (40%), and reported heterosexual transmission (64%). Chinese (27%), Thai (26%), and Indian (11%) were the main ethnic groups. At recruitment, approximately 12% did not have a CD4 count test, and of those tested, the majority had a CD4 count more than 200 cells/ μ L. Nearly half (45%) did not have an HIV viral load test, and of those tested, the majority were below 500 copies/mL. Close to half of the patients (46%) were diagnosed with an AIDS defining illness at recruitment, with tuberculosis being the main illness. Most patients (63%) had been reported to be diagnosed with HIV for less than 6 years when recruited to TAHOD (measured as the time from first reported positive HIV test). Less than 10% of the patients were coinfecting with either hepatitis B or hepatitis C. At recruitment, the majority of patients had normal haemoglobin level. At the start of study followup, most of the patients were on antiretroviral therapy including three or more drugs in combination including at least one nucleoside reverse transcriptase inhibitor (NRTI) and one nonnucleoside reverse transcriptase inhibitor. Over 20% of patients were in a combination with at least one NRTI and a protease inhibitor (PI). All patients were receiving, or started, antiretroviral therapy during followup.

Table 3 summarises univariate and multivariate analyses of factors associated with LTFU using 180 days as cut-off. In univariate analyses, the rate of LTFU was significantly lower in patients with a current CD4 counts above 200 cells/ μ L compared to patients with a CD4 count less than 100 cells/ μ L, but this was not significant in the final multivariate model. In the final multivariate model (Table 3), factors associated

TABLE 2: Patient characteristics.

| Total Characteristics | Number | % |
|--|--------|----|
| Total | 3626 | |
| Sex | | |
| Male | 2567 | 71 |
| Female | 1059 | 29 |
| Current age (years) | | |
| ≤35 | 1383 | 38 |
| 36–45 | 1449 | 40 |
| 46+ | 794 | 22 |
| Reported exposure | | |
| Heterosexual contact | 2337 | 64 |
| Homosexual contact | 749 | 21 |
| Injecting drug use | 263 | 7 |
| Other/unknown | 277 | 8 |
| Ethnicity | | |
| Chinese | 989 | 27 |
| Indian | 390 | 11 |
| Thai | 933 | 26 |
| Other/unknown | 1314 | 36 |
| Baseline CD4 count (cells/μl.) | | |
| ≤100 | 239 | 7 |
| 101–200 | 406 | 11 |
| 201+ | 2531 | 70 |
| Missing | 450 | 12 |
| Baseline HIV RNA (copies/ml) | | |
| ≤500 | 1482 | 41 |
| 501+ | 379 | 10 |
| Missing | 1765 | 49 |
| CDC disease stage at baseline | | |
| Stage A | 1621 | 45 |
| Stage B | 321 | 9 |
| Stage C | 1684 | 46 |
| Tuberculosis diagnosis at baseline | | |
| No | 2758 | 76 |
| Yes | 868 | 24 |
| Time since HIV infection (years) | | |
| ≤5 | 2295 | 63 |
| 6+ | 1246 | 34 |
| Missing | 85 | 2 |
| Hepatitis B infection | | |
| No | 2297 | 63 |
| Yes | 257 | 7 |
| Not tested | 1072 | 30 |
| Hepatitis C infection | | |
| No | 2007 | 55 |
| Yes | 324 | 9 |
| Not tested | 1295 | 36 |
| Anemia at baseline | | |
| No | 2480 | 68 |
| Yes | 597 | 16 |
| Haemoglobin not tested | 567 | 16 |

TABLE 2: Continued.

| Total Characteristics | Number | % |
|---|--------|----|
| Total | 3626 | |
| Antiretroviral treatment at baseline | | |
| 3 + (NRTI + NNRTI) | 2224 | 61 |
| 3 + (NRTI + PI) | 744 | 21 |
| No/mono/double drug | 583 | 16 |
| 3 + (other combination) | 75 | 2 |

Anemia: haemoglobin <13 g/dl (male), <11 g/dl (female); NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

with LTFU included age (younger patients had higher rate of LTFU), current HIV viral load (either patients with HIV viral load ≥ 500 copies/mL or no tests in recent 180 days had higher rate of LTFU), history of HIV infection (patients with shorter history of HIV infection had higher rate of LTFU), hepatitis C infection (patients with positive hepatitis C antibody had higher rate of LTFU), and, finally, current combination of antiretroviral treatment (compared to patients on triple-drug regimen with at least one NRTI and one NNRTI, patients receiving no-, single-, or double-drug antiretroviral therapy, or a triple-drug regimen containing at least one NRTI and one PI, had higher rate of LTFU).

Table 4 shows factors that predict permanent LTFU among patients who had no clinic visit for 180 days and so met our optimal definition of LTFU. In the final multivariate model, patients permanently LTFU were more likely to be older, have not been anemic, have no recent HIV viral load test, have tested negative for hepatitis C infection or have never tested for hepatitis C, and have had more than one episode of previous temporary LTFU.

4. Discussion

We found that an interval of 180 days between clinic visits was the best-performing definition of LTFU based on sensitivity and specificity in identifying true LTFU. By this definition, we observed that approximately one in five patients in our cohort would miss clinic visits for more than 180 days and so become defined as LTFU. Among these patients in our cohort close to half eventually returned to followup, with half becoming truly lost to HIV-related treatment and care.

The 180-day cutoff has been used by other studies as a working definition of LTFU [10, 19–21]. Other intervals have also been proposed as measurements of classifications of LTFU, such as 90 days [8] and 365 days [9]. Regional- and cohort-dependent characteristics, such as scheduled clinic visits, patient burden, and drug availability could result in specific intervals that best categorise patients at risk of LTFU. Nevertheless, a 180-day (or 6-month) cutoff is an appealing and easy-to-apply definition that could be used in different clinical settings in the Asia-Pacific region to flag patients at risk of being permanently lost to treatment and care. Our analyses suggest patients with no clinic visits for six months

TABLE 3: Factors associated with permanent or temporary LTFU, defined as no clinic visit for 180 days, among all patients under followup.

| | Person-years | Number LTFU | Crude Rate ¹ | Adjusted | | | | | | | |
|---|--------------|-------------|-------------------------|----------------|------------------|--------------|---------|------------------|--------------|--------------------|--|
| | | | | 95% CI | IRR ² | 95% CI | P value | IRR ² | 95% CI | P value | |
| Sex | | | | | | | | | | | |
| Male | 5468.1 | 1206 | 22.06 | (20.85, 23.34) | 1.00 | | | | 1.00 | | |
| Female | 2229.2 | 442 | 19.83 | (18.06, 21.77) | 1.10 | (0.98, 1.24) | 0.090 | 1.04 | (0.93, 1.17) | 0.446 | |
| Current age (years) | | | | | | | | | | | |
| ≤35 | 2210.4 | 575 | 26.01 | (23.97, 28.23) | 1.00 | | | 1.00 | | 0.002 ³ | |
| 36~45 | 3320.2 | 718 | 21.62 | (20.10, 23.27) | 0.82 | (0.74, 0.92) | 0.001 | 0.89 | (0.79, 1.00) | 0.050 | |
| 46+ | 2166.6 | 355 | 16.39 | (14.77, 18.18) | 0.69 | (0.60, 0.79) | <0.001 | 0.76 | (0.66, 0.88) | <0.001 | |
| Reported exposure | | | | | | | | | | | |
| Heterosexual contact | 5144.5 | 985 | 19.15 | (17.99, 20.38) | 1.00 | | | 1.00 | | | |
| Homosexual contact | 1707.2 | 344 | 20.15 | (18.13, 22.40) | 1.10 | (0.93, 1.29) | 0.275 | 1.05 | (0.89, 1.25) | 0.540 | |
| Injecting drug use | 344.3 | 125 | 36.31 | (30.47, 43.27) | 1.21 | (0.97, 1.51) | 0.098 | 1.10 | (0.86, 1.40) | 0.437 | |
| Other/unknown | 501.3 | 194 | 38.70 | (33.62, 44.55) | 1.64 | (1.37, 1.98) | <0.001 | 1.56 | (1.29, 1.88) | <0.001 | |
| Current CD4 count (cells/μL) | | | | | | | | | | | |
| ≤100 | 233.7 | 69 | 29.52 | (23.32, 37.38) | 1.00 | | | 1.00 | | | |
| 101–200 | 635.7 | 136 | 21.40 | (18.09, 25.31) | 0.92 | (0.68, 1.22) | 0.551 | 0.96 | (0.72, 1.29) | 0.800 | |
| 201+ | 6327.6 | 1181 | 18.66 | (17.63, 19.76) | 0.75 | (0.58, 0.96) | 0.023 | 0.79 | (0.61, 1.02) | 0.071 | |
| Missing | 500.3 | 262 | 52.37 | (46.40, 59.11) | 1.18 | (0.90, 1.55) | 0.235 | 0.99 | (0.74, 1.31) | 0.922 | |
| Current HIV RNA (copies/ml) | | | | | | | | | | | |
| ≤500 | 4213.7 | 679 | 16.11 | (14.95, 17.37) | 1.00 | | | 1.00 | | 0.021 ³ | |
| 501+ | 537.1 | 158 | 29.42 | (25.17, 34.38) | 1.71 | (1.43, 2.04) | <0.001 | 1.24 | (1.03, 1.51) | 0.026 | |
| Missing | 2946.4 | 811 | 27.52 | (25.69, 29.49) | 1.75 | (1.55, 1.98) | <0.001 | 1.64 | (1.45, 1.86) | <0.001 | |
| CDC disease stage | | | | | | | | | | | |
| Stage A | 3205.1 | 828 | 25.83 | (24.13, 27.65) | 1.00 | | | 1.00 | | | |
| Stage B | 801.6 | 118 | 14.72 | (12.29, 17.63) | 0.93 | (0.76, 1.14) | 0.507 | 0.95 | (0.77, 1.17) | 0.623 | |
| Stage C | 3690.5 | 702 | 19.02 | (17.67, 20.48) | 0.84 | (0.75, 0.93) | 0.001 | 0.92 | (0.82, 1.02) | 0.125 | |
| Tuberculosis diagnosis | | | | | | | | | | | |
| Yes | 1806.7 | 372 | 20.59 | (18.60, 22.79) | 1.00 | | | 1.00 | | | |
| No | 5890.6 | 1276 | 21.66 | (20.51, 22.88) | 1.04 | (0.92, 1.18) | 0.537 | 0.98 | (0.87, 1.12) | 0.801 | |
| Time since HIV infection (years) | | | | | | | | | | | |
| ≤5 | 3477.2 | 785 | 22.58 | (21.05, 24.21) | 1.00 | | | 1.00 | | 0.005 ³ | |
| 6+ | 4115.7 | 844 | 20.51 | (19.17, 21.94) | 0.84 | (0.75, 0.94) | 0.002 | 0.89 | (0.79, 1.00) | 0.048 | |
| Missing | 104.3 | 19 | 18.21 | (11.61, 28.55) | 0.58 | (0.36, 0.94) | 0.027 | 0.49 | (0.30, 0.79) | 0.004 | |
| Hepatitis B infection | | | | | | | | | | | |
| Yes | 584.5 | 112 | 19.16 | (15.92, 23.06) | 1.00 | | | 1.00 | | | |
| No | 5101.9 | 883 | 17.31 | (16.20, 18.49) | 0.93 | (0.76, 1.13) | 0.474 | 0.90 | (0.74, 1.10) | 0.319 | |
| N/A | 2010.8 | 653 | 32.48 | (30.08, 35.06) | 0.98 | (0.80, 1.21) | 0.859 | 1.07 | (0.85, 1.35) | 0.548 | |
| Hepatitis C infection | | | | | | | | | | | |
| Yes | 541.4 | 149 | 27.52 | (23.44, 32.31) | 1.00 | | | 1.00 | | 0.030 ³ | |
| No | 4692.8 | 796 | 16.96 | (15.82, 18.18) | 0.81 | (0.67, 0.98) | 0.029 | 0.81 | (0.67, 0.98) | 0.034 | |
| N/A | 2463.0 | 703 | 28.54 | (26.51, 30.73) | 0.75 | (0.62, 0.91) | 0.004 | 0.77 | (0.63, 0.93) | 0.008 | |
| Current anemia (male < 13 g/dl, female < 11 g/dl) | | | | | | | | | | | |
| Yes | 1021.1 | 155 | 15.18 | (12.97, 17.77) | 1.00 | | | 1.00 | | | |
| No | 5771.6 | 1157 | 20.05 | (18.92, 21.24) | 1.09 | (0.92, 1.30) | 0.302 | 1.11 | (0.94, 1.32) | 0.227 | |
| N/A | 904.5 | 336 | 37.15 | (33.38, 41.34) | 1.31 | (1.07, 1.59) | 0.008 | 1.09 | (0.89, 1.34) | 0.382 | |

TABLE 3: Continued.

| | Person-years | Number LTFU | Crude Rate ¹ | Adjusted | | | | | | |
|--------------------------|--------------|-------------|-------------------------|----------------|------------------|--------------|---------|------------------|--------------|--------------------|
| | | | | 95% CI | IRR ² | 95% CI | P value | IRR ² | 95% CI | P value |
| Current ART ⁴ | | | | | | | | | | |
| 3 + (NRTNRTI) | 4830.8 | 942 | 19.50 | (18.29, 20.79) | 1.00 | | | 1.00 | | 0.001 ³ |
| 3 + (NRTI + PI) | 1898.3 | 377 | 19.86 | (17.95, 21.97) | 1.21 | (1.06, 1.38) | 0.005 | 1.22 | (1.07, 1.39) | 0.003 |
| No/mono/double ARV | 762.7 | 300 | 39.33 | (35.12, 44.05) | 2.18 | (1.90, 2.50) | <0.001 | 1.92 | (1.66, 2.22) | <0.001 |
| 3 + (other combination) | 205.4 | 29 | 14.12 | (9.81, 20.32) | 0.95 | (0.65, 1.38) | 0.786 | 1.01 | (0.69, 1.47) | 0.975 |

(1) Crude rate, per 100 person-years.

(2) Stratified by TAHOD sites.

(3) Overall for test for trend (ordinal categorical covariates) or for homogeneity (nominal categorical covariates).

(4) ART: NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

are at high risk of being permanently lost and should be aggressively traced.

Chi et al. also found that a cutoff of 180 days was optimal to define LTFU after analysing data from the Africa, Asia, and Latin America regions of the IeDEA collaboration (including data from our cohort) [22]. There are some methodological differences between our analyses, principally regarding minimum numbers of patients for site inclusion. Chi et al. found quite extensive heterogeneity between sites, something we also found to a lesser extent. However, it is nevertheless reassuring that we found a similar optimal cutoff of 180 days without clinic visits to define LTFU. With rapid scaling up of antiretroviral treatment taking place globally, there is a need to adopt a universal consistent definition of LTFU, or a general algorithm to define cutoffs, to evaluate HIV treatment programs in different regions [6, 7, 19].

Over one in five patients in our cohort failed to come to clinic for more than 180 days in a given year. Similar rates have also been found in patients from Africa [3, 11]. However, the LTFU rate was lower in EuroSIDA [23], a large prospective cohort study with HIV-infected patients mainly from Europe (using one year as a cutoff). Approximately half of the patients who experienced LTFU in our study later came back to clinic, and patients who had a previous episode of LTFU were more likely to prove to be true LTFU, similar to previous findings [18].

We found that younger patients, patients infected with hepatitis C, and patients with detectable or unmeasured viral load were more likely to experience LTFU. These findings are all consistent with previous study findings [10, 11, 24–26]. Patients with undetectable viral load are likely to be motivated and adherent to antiretroviral treatment and thus remain in care. Among those patients who experienced LTFU, we found that those who tested negative for hepatitis C infection or were never tested for hepatitis C were more likely to be permanently LTFU. This finding seems counterintuitive, but it might be that patients who have tested positive for hepatitis C receive more medical attention from their clinicians and thus prove less likely to be permanently

LTFU. Among patients identified as LTFU, anemic patients were also more likely to be permanently lost to treatment and care. Anemia has been shown to be a strong prognostic marker for HIV disease progression and survival [27], which could, at least in part, explain these patients failing to return to followup.

Compared to patients on NNRTI-based regimen, patients receiving no-, single-, or double-drug antiretroviral therapy or a triple-drug regimen containing PI were more likely to experience LTFU. The reasons for this are not clear. The greater loss to followup may be associated with increased drug toxicity, either resulting in a patient receiving mono- or dual therapy or from receiving a PI. Patients receiving PI-based regimens are also those who are more likely to be on a second line regimen, a regimen that may be substantially more expensive than first line. In the Asia Pacific region, out-of-pocket expenses are needed to pay for treatment in some clinics. Hence, the lost to followup may be associated with drug availability or affordability. It is worth noting that patients receiving mono- or dual therapy, or a PI based regimen, were also associated with being less likely to be permanently lost to followup, that is to say more likely to return to clinic (albeit not quite statistically significantly so). This possibly supports the idea of these regimens being associated with short-term drug availability or affordability issues. Unfortunately, data are not available to address this issue in any greater detail.

It has been shown that, in resource-limited settings, predominantly in Africa, patients who are LTFU have a much poorer prognosis than patients who remain in followup [5]. In part, this is due to a proportion of patients who die not having vital status information updated at their treatment site. The extent to which this occurs in TAHOD is uncertain. While it seems likely that at least some patients who are LTFU have died without this information reaching the site, the lack of association between key measures of HIV disease progression, such as CD4 count and AIDS defining illnesses, and LTFU suggests it may be lower than in African settings. However, this association between LTFU and poorer prognosis underpins the need for consistent definitions of

TABLE 4: Factors that predict permanent LTFU in patients without a clinic visit for 180 days.

| | Number | True loss | % | OR ¹ | 95% CI | P value | Adjusted OR ¹ | 95% CI | P value |
|---|--------|-----------|------|-----------------|--------------|---------|--------------------------|--------------|---------------------|
| Sex | | | | | | | | | |
| Male | 1206 | 584 | 48.4 | 1.00 | | | 1.00 | | |
| Female | 442 | 209 | 47.3 | 0.89 | (0.69, 1.15) | 0.359 | 0.80 | (0.61, 1.05) | 0.104 |
| Current age (years) | | | | | | | | | |
| ≤35 | 568 | 278 | 48.9 | 1.00 | | | 1.00 | | 0.097 ² |
| 36~45 | 717 | 340 | 47.4 | 1.33 | (1.03, 1.71) | 0.031 | 1.31 | (1.00, 1.72) | 0.050 |
| 46+ | 363 | 175 | 48.2 | 1.27 | (0.94, 1.72) | 0.118 | 1.28 | (0.93, 1.77) | 0.128 |
| Reported exposure | | | | | | | | | |
| Heterosexual contact | 985 | 443 | 45.0 | 1.00 | | | 1.00 | | |
| Homosexual contact | 344 | 199 | 57.8 | 1.12 | (0.78, 1.60) | 0.532 | 1.24 | (0.85, 1.81) | 0.262 |
| Injecting drug use | 125 | 55 | 44.0 | 1.01 | (0.59, 1.73) | 0.969 | 1.32 | (0.72, 2.41) | 0.364 |
| Other/unknown | 194 | 96 | 49.5 | 1.07 | (0.69, 1.64) | 0.773 | 1.22 | (0.78, 1.93) | 0.382 |
| Current CD4 count (cells/ μ L) | | | | | | | | | |
| ≤100 | 58 | 36 | 62.1 | 1.00 | | | 1.00 | | |
| 101–200 | 129 | 66 | 51.2 | 0.76 | (0.36, 1.60) | 0.471 | 0.99 | (0.47, 2.13) | 0.989 |
| 201+ | 1068 | 465 | 43.5 | 0.62 | (0.33, 1.18) | 0.144 | 0.82 | (0.42, 1.59) | 0.551 |
| Missing | 393 | 226 | 57.5 | 1.50 | (0.77, 2.93) | 0.238 | 1.18 | (0.58, 2.42) | 0.649 |
| Current HIV RNA (copies/mL) | | | | | | | | | |
| ≤500 | 598 | 230 | 38.5 | 1.00 | | | 1.00 | | 0.011 ² |
| 501+ | 153 | 78 | 51.0 | 1.02 | (0.68, 1.52) | 0.924 | 0.94 | (0.62, 1.42) | 0.767 |
| Missing | 897 | 485 | 54.1 | 2.13 | (1.63, 2.80) | <0.001 | 1.54 | (1.13, 2.09) | 0.006 |
| CDC disease stage | | | | | | | | | |
| Stage A | 828 | 413 | 49.9 | 1.00 | | | 1.00 | | |
| Stage B | 121 | 54 | 44.6 | 0.77 | (0.48, 1.22) | 0.258 | 0.70 | (0.43, 1.14) | 0.154 |
| Stage C | 699 | 326 | 46.6 | 1.00 | (0.78, 1.27) | 0.975 | 1.05 | (0.81, 1.36) | 0.702 |
| Tuberculosis diagnosis | | | | | | | | | |
| Yes | 361 | 186 | 51.5 | 1.00 | | | 1.00 | | |
| No | 1287 | 607 | 47.2 | 0.87 | (0.66, 1.16) | 0.342 | 0.85 | (0.63, 1.15) | 0.297 |
| Time since HIV infection (years) | | | | | | | | | |
| ≤5 | 771 | 400 | 51.9 | 1.00 | | | 1.00 | | |
| 6+ | 858 | 389 | 45.3 | 1.25 | (0.98, 1.60) | 0.076 | 1.03 | (0.79, 1.34) | 0.835 |
| Missing | 19 | 4 | 21.1 | 0.37 | (0.12, 1.17) | 0.091 | 0.43 | (0.13, 1.43) | 0.170 |
| Hepatitis B infection | | | | | | | | | |
| Yes | 112 | 47 | 42.0 | 1.00 | | | 1.00 | | |
| No | 883 | 431 | 48.8 | 1.30 | (0.84, 2.03) | 0.243 | 1.35 | (0.84, 2.16) | 0.222 |
| N/A | 653 | 315 | 48.2 | 1.31 | (0.82, 2.09) | 0.253 | 1.03 | (0.60, 1.76) | 0.908 |
| Hepatitis C infection | | | | | | | | | |
| Yes | 149 | 66 | 44.3 | 1.00 | | | 1.00 | | 0.004 ² |
| No | 796 | 376 | 47.2 | 1.57 | (1.01, 2.45) | 0.046 | 1.66 | (1.04, 2.66) | 0.034 |
| N/A | 703 | 351 | 49.9 | 1.96 | (1.26, 3.05) | 0.003 | 2.16 | (1.35, 3.46) | 0.001 |
| Current anemia (male < 13 g/dL, female < 11 g/dL) | | | | | | | | | |
| Yes | 141 | 87 | 61.7 | 1.00 | | | 1.00 | | <0.001 ² |
| No | 1065 | 456 | 42.8 | 0.53 | (0.35, 0.81) | 0.003 | 0.50 | (0.32, 0.76) | 0.001 |
| N/A | 442 | 250 | 56.6 | 1.15 | (0.73, 1.81) | 0.549 | 0.78 | (0.49, 1.26) | 0.310 |
| Current ART** | | | | | | | | | |
| 3 + (NRTI + NNRTI) | 911 | 404 | 44.3 | 1.00 | | | 1.00 | | |
| 3 + (NRTI + PI) | 356 | 167 | 46.9 | 0.76 | (0.57, 1.02) | 0.072 | 0.74 | (0.54, 1.01) | 0.057 |
| No/mono/double ARV | 352 | 209 | 59.4 | 0.93 | (0.69, 1.26) | 0.644 | 0.78 | (0.57, 1.08) | 0.137 |
| 3 + (other combination) | 29 | 13 | 44.8 | 0.89 | (0.40, 1.98) | 0.770 | 0.85 | (0.38, 1.94) | 0.707 |

TABLE 4: Continued.

| | Number | True loss | % | OR ¹ | 95% CI | P value | Adjusted OR ¹ | 95% CI | P value |
|------------------------------------|--------|-----------|------|-----------------|----------------|---------|--------------------------|----------------|---------------------|
| Previous episode of temporary LTFU | | | | | | | | | |
| None | 1298 | 589 | 45.4 | 1.00 | | | 1.00 | | <0.001 ² |
| Once | 296 | 158 | 53.4 | 2.79 | (2.05, 3.80) | <0.001 | 2.71 | (1.97, 3.72) | <0.001 |
| Twice | 54 | 46 | 85.2 | 31.76 | (13.91, 72.52) | <0.001 | 27.75 | (12.03, 64.01) | <0.001 |

(1) Stratified by TAHOD sites.

(2) Overall for test for trend (ordinal categorical covariates) or for homogeneity (nominal categorical covariates).

(3) ART: NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

LTFU in research cohort studies, and where there are possible active patient tracing strategies or at least sampling-based approaches [28] to ensure comparability of results across studies and settings.

Several limitations should be considered in interpreting the results in this paper. First, TAHOD participating sites are generally urban referral centres, and the patients recruited in TAHOD were those regularly attending a given TAHOD site. Hence, TAHOD patients are not representative of all HIV-infected patients in the Asia and Pacific region. The overall rate of LTFU we saw in our study is therefore likely to be an underestimate of rates across the region. However, the effect of these sampling biases on the optimal definition of LTFU and on the covariate analyses is arguably less strong. It is reassuring that our estimate of the optimal definition of LTFU is consistent with that seen across Africa and Latin America [22]. Second, since antiretroviral treatment has become more decentralised and available in distant or rural communities with rapid scale-up programs, patients might choose to receive treatment and care locally rather than at tertiary and referral centres [29, 30]. Consequently, patients may have been retained in care but not necessarily in the clinics involved in this study. Information on referral to other health facility was only recently included in the data collection, so we could not further verify if patients were retained in care or truly loss to health services. Third, we do not collect data on the measures TAHOD sites undertake to routinely trace patients who are LTFU. These measures differ across sites according to local practices and conditions. Effective patient tracking and recording are essential to program evaluation and maintenance of treatment and care [1, 18]. What patient tracking measures are effective in retaining patients in treatment and care in the Asia-Pacific region is an area that deserves further research. We also do not have data on transportation [31], social and economic status [32], pregnancy for women [10], and community support [33], all of which have been found to be important determinants of LTFU. Lastly, the patients included in this study were all receiving, or started, antiretroviral treatment and had clinical assessments. Consequently, the results cannot be extrapolated to patients not yet initiated on antiretroviral therapy. Research into followup among HIV-infected patients not receiving antiretroviral treatment in the Asia-Pacific region needs to be considered [34–36], particularly in the context of the move to start treatment earlier.

5. Conclusion

With rapid scaleup of antiretroviral treatment, it is essential to study factors that predict loss to followup and identify patients at risk of loss to treatment and care, particularly in resource-limited settings. At the treatment and care level, this can maintain efficacy of antiretroviral therapy and avoid adverse events. At the program evaluation level, the impact of loss to followup on overall treatment outcome, disease progression, and survival can then be accounted for with appropriate statistical adjustments. Collaboration with HIV treatment programs in other regions in studies on LTFU and in particular standardisation of LTFU definitions are essential for reporting and program evaluation.

Acknowledgments

The TREAT Asia HIV Observational Database and the Australian HIV Observational Database are part of the Asia Pacific HIV Observational Database and are initiatives of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the following institutes of the US National Institutes of Health (NIH): National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), the Office of the Director (OD), and the National Cancer Institute (NCI), as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (Grant no. U01AI069907). Additional support is provided by the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds and from the Austrian AIDS Life Association (AALA). The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

References

- [1] R. P. Dalal, C. MacPhail, M. Mqhayi et al., “Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 47, no. 1, pp. 101–107, 2008.

- [2] A. T. Brennan, M. Maskew, I. Sanne, and M. P. Fox, "The importance of clinic attendance in the first six months on antiretroviral treatment: a retrospective analysis at a large public sector HIV clinic in South Africa," *Journal of the International AIDS Society*, vol. 13, no. 1, article 49, 2010.
- [3] H. Bygrave, K. Kranzer, K. Hilderbrand et al., "Trends in loss to follow-up among migrant workers on antiretroviral therapy in a community cohort in Lesotho," *PLoS ONE*, vol. 5, no. 10, Article ID e13198, 2010.
- [4] M. W. G. Brinkhof, B. D. Spycher, C. Yiannoutsos et al., "Adjusting mortality for loss to follow-up: analysis of five art programmes in sub-saharan africa," *PLoS ONE*, vol. 5, no. 11, Article ID e14149, 2010.
- [5] M. W. G. Brinkhof, M. Pujades-Rodriguez, and M. Egger, "Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis," *PLoS ONE*, vol. 4, no. 6, Article ID e5790, 2009.
- [6] B. H. Chi, R. A. Cantrell, A. Mwango et al., "An empirical approach to defining loss to follow-up among patients enrolled in antiretroviral treatment programs," *American Journal of Epidemiology*, vol. 171, no. 8, pp. 924–931, 2010.
- [7] M. Egger, B. D. Spycher, J. Sidle et al., "Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa," *PLoS Medicine*, vol. 8, no. 1, article e1000390, 2011.
- [8] K. Wools-Kaloustian, S. Kimaiyo, L. Diero et al., "Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya," *AIDS*, vol. 20, no. 1, pp. 41–48, 2006.
- [9] P. Braitstein, M. W. Brinkhof, F. Dabis et al., "Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries," *The Lancet*, vol. 367, no. 9513, pp. 817–824, 2006.
- [10] B. Wang, E. Losina, R. Stark et al., "Loss to follow-up in a community clinic in South Africa-roles of gender, pregnancy and CD4 count," *South African Medical Journal*, vol. 101, no. 4, pp. 253–257, 2011.
- [11] V. Ochieng-Ooko, D. Ochieng, J. E. Sidle et al., "Influence of gender on loss to follow-up in a large HIV treatment programme in western kenya," *Bulletin of the World Health Organization*, vol. 88, no. 9, pp. 681–688, 2010.
- [12] R. Weigel, M. Hochgesang, M. W.G. Brinkhof et al., "Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi," *BMC Infectious Diseases*, vol. 11, article 31, 2011.
- [13] O. Keiser, B. H. Chi, T. Gsponer et al., "Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa," *AIDS*, vol. 25, no. 14, pp. 1761–1769, 2011.
- [14] S. Thai, O. Koole, P. Un et al., "Five-year experience with scaling-up access to antiretroviral treatment in an HIV care programme in Cambodia," *Tropical Medicine and International Health*, vol. 14, no. 9, pp. 1048–1058, 2009.
- [15] P. L. Toro, M. Kataly, R. J. Carter et al., "Initiation of antiretroviral therapy among pregnant women in resource-limited countries: CD4+ cell count response and program retention," *AIDS*, vol. 24, no. 4, pp. 515–524, 2010.
- [16] M. Panditrao, S. Darak, V. Kulkarni, S. Kulkarni, and R. Parchure, "Socio-demographic factors associated with loss to follow-up of HIV-infected women attending a private sector PMTCT program in Maharashtra, India," *AIDS Care*, vol. 23, no. 5, pp. 593–600, 2011.
- [17] J. Zhou, N. Kumarasamy, F. Zhang et al., "Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD)," *HIV Medicine*, vol. 6, no. 3, pp. 216–223, 2005.
- [18] T. Hill, L. Bansi, C. Sabin et al., "Data linkage reduces loss to follow-up in an observational HIV cohort study," *Journal of Clinical Epidemiology*, vol. 63, no. 10, pp. 1101–1109, 2010.
- [19] M. W. G. Brinkhof, F. Dabis, L. Myer et al., "Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries," *Bulletin of the World Health Organization*, vol. 86, no. 7, pp. 559–567, 2008.
- [20] E. H. Geng, N. Emenyonu, M. B. Bwana, D. V. Glidden, and J. N. Martin, "Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa," *Journal of the American Medical Association*, vol. 300, no. 5, pp. 506–507, 2008.
- [21] C. Cesar, B. E. Shepherd, A. J. Krolewiecki et al., "Rates and reasons for early change of first HAART in HIV-1-infected patients in 7 sites throughout the Caribbean and Latin America," *PLoS ONE*, vol. 5, no. 6, Article ID e10490, 2010.
- [22] B. H. Chi, C. T. Yiannoutsos, A. O. Westfall et al., "Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America," *PLoS Medicine*, vol. 8, no. 10, article e1001111, 2011.
- [23] A. Mocroft, O. Kirk, P. Aldins et al., "Loss to follow-up in an international, multicentre observational study," *HIV Medicine*, vol. 9, no. 5, pp. 261–269, 2008.
- [24] R. Zachariah, K. Tayler-Smith, M. Manzi et al., "Retention and attrition during the preparation phase and after start of antiretroviral treatment in Thyolo, Malawi, and Kibera, Kenya: implications for programmes?" *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 105, no. 8, pp. 421–430, 2011.
- [25] T. Hill, L. Bansi, C. Sabin et al., "Data linkage reduces loss to follow-up in an observational HIV cohort study," *Journal of Clinical Epidemiology*, vol. 63, no. 10, pp. 1101–1109, 2010.
- [26] A. Mocroft, O. Kirk, P. Aldins et al., "Loss to follow-up in an international, multicentre observational study," *HIV Medicine*, vol. 9, no. 5, pp. 261–269, 2008.
- [27] J. D. Lundgren and A. Mocroft, "Anemia and survival in human immunodeficiency virus," *Clinical Infectious Diseases*, vol. 37, no. 4, pp. s297–s303, 2003.
- [28] C. T. Yiannoutsos, M. W. An, C. E. Frangakis et al., "Sampling-based approaches to improve estimation of mortality among patient dropouts: experience from a large PEPFAR-funded program in Western Kenya," *PLoS ONE*, vol. 3, no. 12, Article ID e3843, 2008.
- [29] M. Bedelu, N. Ford, K. Hilderbrand, and H. Reuter, "Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care," *Journal of Infectious Diseases*, vol. 196, no. 3, pp. S464–S468, 2007.
- [30] A. K. Chan, G. Mateyu, A. Jahn et al., "Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model," *Tropical Medicine and International Health*, vol. 15, supplement 1, pp. 90–97, 2010.
- [31] E. H. Geng, D. R. Bangsberg, N. Musunguzi et al., "Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach," *Journal of Acquired Immune Deficiency Syndromes*, vol. 53, no. 3, pp. 405–411, 2010.
- [32] M. Maskew, P. MacPhail, C. Menezes, and D. Rubel, "Lost to follow up—contributing factors and challenges in South

- African patients on antiretroviral therapy," *South African Medical Journal*, vol. 97, no. 9, pp. 853–857, 2007.
- [33] N. C. Ware, J. Idoko, S. Kaaya et al., "Explaining adherence success in sub-Saharan Africa: an ethnographic study," *PLoS Medicine*, vol. 6, no. 1, Article ID e1000011, pp. 0039–0047, 2009.
- [34] E. H. Geng, D. Nash, A. Kambugu et al., "Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions," *Current HIV/AIDS Reports*, vol. 7, no. 4, pp. 234–244, 2010.
- [35] B. Amuron, G. Namara, J. Birungi et al., "Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda," *BMC Public Health*, vol. 9, article 290, 2009.
- [36] T. Togun, I. Peterson, S. Jaffar et al., "Pre-treatment mortality and loss-to-follow-up in HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients eligible for antiretroviral therapy in The Gambia, West Africa," *AIDS Research and Therapy*, vol. 8, no. 1, p. 24, 2011.

ORIGINAL ARTICLE

Interim FDG-PET/CT as a predictor of prognosis for HIV-related malignant lymphoma: Preliminary study

Ryogo Minamimoto¹, Junko Tanuma², Miyako Morooka¹, Kimiteru Ito³, Momoko Okasaki¹, Yoko Miyata¹, Takuro Shimbo⁴, Shinichi Oka², Kazuo Kubota¹

1. Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan. 2. AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan. 3. Department of Radiology, National Center of Neurology and Psychiatry, Tokyo, Japan. 4. Department of Clinical Research and Informatics, National Center for Global Health and Medicine, Tokyo, Japan

Correspondence: Ryogo Minamimoto. Address: Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjyuku-ku, Tokyo 162-8655, Japan.

E-mail: ryogominamimoto@yahoo.co.jp

Received: December 13, 2012

Accepted: January 7, 2013

Online Published: January 9, 2013

DOI: 10.5430/jst.v3n2p1

URL: <http://dx.doi.org/10.5430/jst.v3n2p1>

Abstract

Object: The aim of this retrospective study was to clarify the potential of fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) for predicting prognosis in HIV-related malignant lymphoma (ML).

Methods: Participants comprised 24 patients (23 men, 1 woman; mean age, 42.2 years; range, 25-66 years) with histologically proven ML, classified as either diffuse large B-cell lymphoma (DLBCL) or Burkitt lymphoma according to the classification of the World Health Organization. We compared relationships between overall survival (OS) and several indices, including FDG uptake into the lesion site on pretreatment PET and findings on interim PET. Diagnostic criteria for response evaluation followed International Harmonization Project criteria.

Results: Negative findings on interim PET were associated with significantly longer OS (932±549 days) compared to positive cases (454±442 days, $p=0.043$). Cox regression analysis showed strong prognostic influences of interim PET findings (Hazard ratio 4.57, 95%CI 0.88-23.73) and Eastern Cooperative Oncology Group performance status (Hazard ratio 10.52, 95%CI 1.26-87.82) on OS. No other indices showed significant relationships with OS. No significant correlation was confirmed between OS and both age and lesion uptake of FDG on pretreatment PET.

Conclusion: HIV-related ML patients with negative findings on interim FDG-PET showed longer OS than patients with positive findings. Interim FDG-PET offers a predictor of prognosis for HIV-related ML.

Key words

Fluorodeoxyglucose, Positron emission tomography, HIV, Lymphoma, Overall survival, Interim positron emission tomography

1 Introduction

Highly active antiretroviral therapy (HAART) has made a substantial impact on the disease spectrum and decreasing mortality rate among HIV-infected patients ^[1]. Improved prognosis among HIV-infected patients has resulted from

decreases in the incidence of opportunistic infections, but a malignant complication due to HIV infection is still increasing [2]. Non-Hodgkin's lymphoma (NHL) is extremely common, along with Kaposi sarcoma and Hodgkin's disease, as HIV-related malignancies, and the incidence of developing lymphoma is about 60-fold higher in patients with AIDS than in the general population [3,4]. HIV-related malignant lymphoma (ML) is still a leading cause of mortality in HIV-infected patients, despite the improvements achieved with HAART.

HIV-related ML usually shows an aggressive histological subtype, such as diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, and is frequently diagnosed at a relatively advanced stage. This malignancy tends to involve extranodal sites, and the incidences of central nervous system (CNS) and bone marrow invasion are higher than with non-HIV-related ML [5]. Another distinctive characteristic of HIV-related ML is that CD4 counts and levels of HIV plasma RNA are associated with prognosis [6].

Positron emission tomography (PET) is a noninvasive, quantitative imaging modality that allows visualization of physiological and biological processes. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is useful for management of ML in terms of staging, treatment response and predicting prognosis [7]. Several reports have evaluated findings from FDG-PET/CT in HIV-positive patients [8,9], and the potential of FDG PET/CT for HIV-related malignancy has been reviewed [5,10]. However, the role of FDG-PET/CT in HIV-associated lymphomas is still very poorly studied [11]. This study aimed to clarify the potential of FDG-PET/CT for predicting the prognosis of HIV-related ML.

2 Methods

2.1 Study design

All study protocols in this retrospective observation study were approved by the institutional review board. We retrospectively examined 24 HIV-infected patients with histologically confirmed ML classified as either DLBCL or Burkitt lymphoma in accordance with the classification of the World Health Organization (WHO), who had undergone FDG-PET/CT between July 2005 and September 2009.

Before initiation of therapy, all patients were staged by clinical examination, laboratory screening, contrast-enhanced CT of the thorax and abdomen, and pathological diagnosis based on lesion and bone marrow biopsies. Among the 24 patients included in this study, 15 patients underwent baseline FDG-PET/CT for staging and confirmation of FDG uptake. The other 9 patients did not undergo baseline FDG-PET/CT, because these cases had an aggressive lymphoma which had no time to undergo FDG-PET/CT scan before immediate treatment. Twenty patients had received first-line chemotherapy at the time of interim PET imaging, while 4 patients had received second-line chemotherapy. The chemotherapy regimens used were R-CHOP (n=9), RHyperCVAD (n=7), HyperCVAD (n=3), EPOCH (n=1), modEHSAP (n=1), EHSAP and DICE (n=1), or R-ESHAP (n=2). All patients underwent FDG-PET/CT during treatment, which was scheduled for before the start of the next course of chemotherapy.

2.2 PET/CT imaging

The ^{18}F -FDG used in this study was synthesized with an in-house cyclotron and an automated synthesis system (F100; Sumitomo Heavy Industries) following authorized procedures. All subjects fasted for 5 h before receiving an intravenous injection of 370 MBq of ^{18}F -FDG, and serum glucose levels measured at the time of ^{18}F -FDG injection were <150 mg/dL in all examinations. PET/CT images were obtained using a PET/CT system (Biograph 16; Siemens) consisting of a PET scanner and multidetector-row CT (16 detectors), and measuring from the vertex to the mid-thigh or knee joints 60 min after intravenous injection of ^{18}F -FDG. Low-dose CT was performed first and used for attenuation correction and image fusion. Emission images were acquired in 3-dimensional mode for 2 min per bed position. Data from PET were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets).

2.3 Evaluation of pretreatment and interim PET images

Pretreatment FDG-PET/CT was performed for 15 cases, and the maximum standardized uptake value (SUV) of the most FDG-avid lesion was measured. Interim FDG-PET scan was performed after 1 cycle of chemotherapy in 4 cases, after 2 cycles of chemotherapy in 10 cases, after 3 cycles of chemotherapy in 7 cases and after 4 cycles of chemotherapy in 3 cases. Image evaluation was performed by physicians with >5 years of experience in nuclear medicine. Diagnostic criteria for response evaluation followed International Harmonization Project criteria^[12].

2.4 Statistical analysis

Data were expressed as mean \pm SD. Mann-Whitney's U-test was used for evaluating differences in diagnostic performance between DLBCL and Burkitt lymphoma. Overall survival (OS) was defined as the interval from interim PET to death from any cause. Univariate analysis by proportional hazards (Cox) regression was used to assess the value of prognostic factors for predicting OS. Survival curves were calculated according to the methods of Kaplan and Meier^[13], with differences between groups analyzed using the log-rank test. Values of $p < 0.05$ were considered statistically significant.

Table 1. Patient characteristics

| Characteristic | Total | DLBCL | Burkitt | UN |
|---|--------------|--------------|--------------|----|
| Patients | 24 | 13 | 11 | — |
| Male | 23 | 13 | 10 | — |
| Median age, y (range) | 42.2 (25-66) | 45.6 (27-66) | 38.3 (25-61) | — |
| ECOG performance status 3-4 | 10 | 5 | 5 | 1 |
| Stage III/IV | 17/24 | 6/13 | 11/11 | — |
| Extranodal sites | 22 | 12 | 10 | — |
| Bonemarrow involvement | 9 | 0 | 9 | 3 |
| CNS involvement | 4 | 0 | 4 | — |
| Median Soluble IL-2 level | 1,649 | 1,239 | 2,184 | 1 |
| Median LDH level | 1,779 | 273 | 3,149 | — |
| LDH level (<400 IU/L) | 20 | 9 | 11 | 3 |
| Median CD4 count (cells/mm ³) | 204 | 149 | 259 | 2 |
| 17 - 100 cells/L | 8 | 6 | 2 | — |
| 101 - 493 cells/L | 14 | 5 | 9 | — |
| Median HIV viral load (range) | 789,060 | 231,060 | 1,347,060 | 2 |
| cART naive | 15 | 6 | 9 | — |
| EBER positive in biopsy tissue sample | 12 | 6 | 6 | 6 |
| CD20 positive | 22 | 12 | 10 | — |

DLBCL: diffuse large B cell lymphoma, UN: unknown, ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase, CNS: central nervous system, IL-2: interleukin-2 receptor, cART, combination antiretroviral therapy, EBER: Epstein-Barr virus-encoded small RNA.

3 Results

3.1 Patient characteristics

We retrospectively examined 24 HIV-infected patients (23 men, 1 woman; mean age, 42.2 years; range, 25-66 years). Patient characteristics are summarized in Table 1. After a median follow-up of 24 months (range, 2-57 months), 17 of 24 patients remained alive and 7 had died due to progression of ML. Patient characteristics are shown in Table 1. According to the malignancy criteria of the WHO, ML in the 24 HIV-infected patients was classified in DLBCL (n=13) or Burkitt lymphoma (n=11). Burkitt lymphoma in HIV-infected patients typically shows a more advanced stage at first diagnosis,

and a high incidence of bone marrow and CNS involvements. Mean CD4 counts, HIV viral load and Lactate Dehydrogenase (LDH) level were higher in Burkitt lymphoma than in DLBCL, however statistical significance was confirmed in LDH alone.

3.2 FDG-PET/CT images

Figures 1 and 2 show the paradigm for FDG-PET/CT during the course of treatment for ML in HIV-infected patients (Figures 1 and 2). Pretreatment FDG-PET/CT was performed for 15 patients, comprising 12 patients for initial staging and 3 patients for restaging suspected ML recurrence. Interim FDG-PET/CT for the evaluation of therapeutic responses was performed in all 24 cases, and 10 cases were evaluated as “positive interim PET” and 14 cases were evaluated as “negative interim PET”. Mean interval between pretreatment PET and interim PET was 56.4 ± 21.9 days (range, 27-99 days).

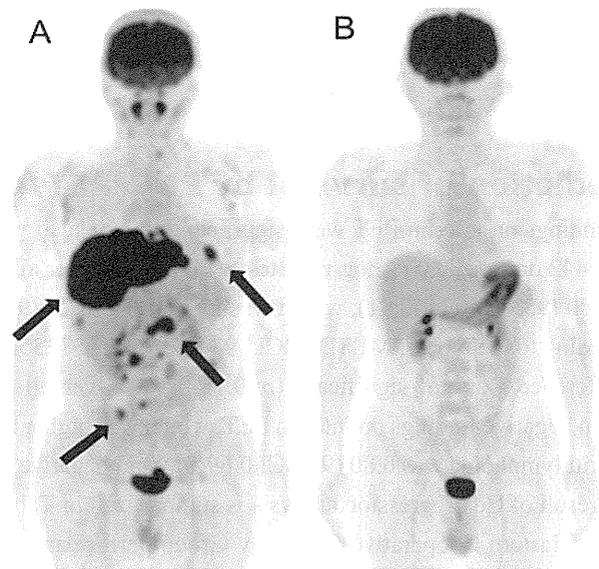


Figure 1. A. The pretreatment PET/CT shows multiple FDG avid lesions (arrows) for HIV related ML (DLBCL) and small focal FDG uptakes. B. Interim PET/CT shows disappearance of all FDG avid lesions. Long OS with 1,328 days was confirmed in this case.

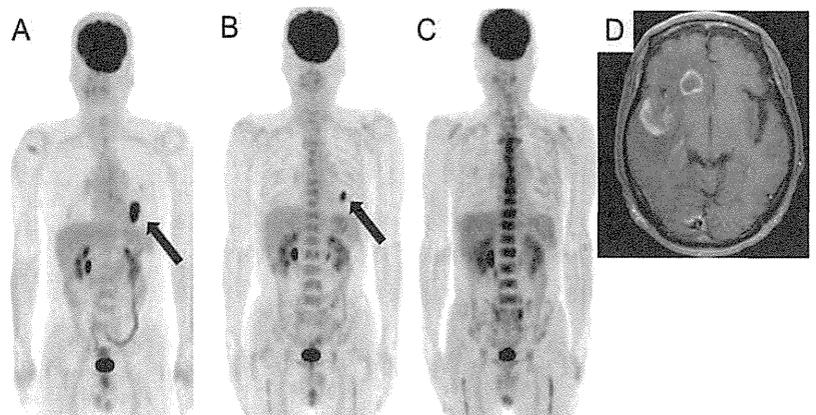


Figure 2. A. The pretreatment PET/CT shows FDG avid lesions at the left lung. B. Interim PET/CT shows residual FDG uptake at the lung. C. Follow-up PET/CT shows disappearance of the lesions but CNS ML was confirmed. This case showed short OS (134 days).

Mean SUVmax of FDG uptake by lymphoma lesions was 15.6 ± 7.3 in ML patients on pretreatment FDG-PET/CT. No significant difference in FDG accumulation was seen between DLBCL ($n=10$, 15.7 ± 8.0) and Burkitt lymphoma ($n=5$, 15.3 ± 5.3).

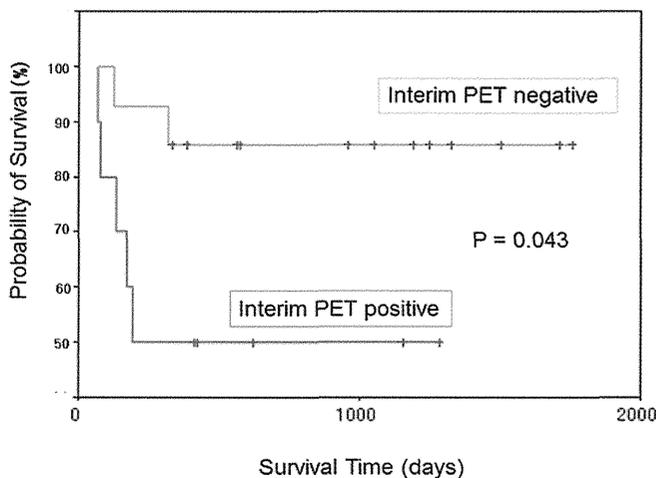


Figure 3. Kaplan-Meier Survival Estimates: Negative findings on interim PET showed longer OS compared with positive cases ($p=0.043$). Over all two year survival rate of negative findings on interim PET was 80%, which was higher than 29% in positive cases

3.3 Prediction of survival by FDG-PET/CT and other indices

Negative findings on interim PET were significantly associated with longer OS (932 ± 549 days) compared with positive cases (454 ± 442 days; $p=0.043$, log-rank test) (Figure 3). Over all two year survival rate of negative findings on interim PET was 0.80 (95%CI 0.69-0.91), which was higher than 0.29 (95%CI 0.16-0.41) in positive cases. A similar trend was found according to the type of ML (DLBCL, 934 ± 593 vs. 557 ± 556 days; Burkitt lymphoma, 931 ± 550 vs. 229 ± 136 days), but the difference was not significant ($p=0.15-0.16$). Over all two year survival rate in DLBCL was 0.80 (95%CI 0.69-0.91) in negative findings on interim PET, which was higher than 0.40 (95%CI 0.27-0.53). Over all two year survival rate in Burkitt lymphoma was 0.80 (95%CI 0.69-0.91) in negative findings on interim PET and no alive patient in positive cases. The result of Cox regression analysis is summarized in Table 2. Cox regression analysis showed strong prognostic influences of Eastern Cooperative Oncology Group performance status (ECOG-PS) ($p=0.03$) and interim PET findings ($p=0.07$) in OS.

Table 2. Univariate analysis of OS to pretreatment prognostic factors and interim PET/CT interpretation

| Index | HR | 95% CI for HR | P value |
|--|-------|---------------|---------|
| Age ≥ 40 vs. < 40 | 1.37 | 0.28 - 0.68 | 0.704 |
| ECOG performance status 2-4 vs. 1 | 10.52 | 1.26 - 87.82 | 0.030 |
| Stage III/IV vs. I/II | 3.91 | 0.06 - 27.84 | 0.274 |
| Bone marrow involvement | 1.17 | 0.24 - 5.83 | 0.844 |
| CNS involvement | 2.21 | 0.43 - 11.52 | 0.346 |
| Bulky mass | 1.13 | 0.21 - 6.17 | 0.888 |
| Soluble interleukin-2 receptor ≥ 1000 vs. < 1000 | 2.27 | 0.42 - 12.46 | 0.344 |
| CD4 count, cells/L (cells/mm ³) ≥ 100 vs. < 100 | 0.47 | 0.10 - 2.36 | 0.362 |
| HIV viral load | 2.33 | 0.27 - 19.98 | 0.440 |
| LDH level (< 400 IU/L) | 0.47 | 0.09 - 2.58 | 0.385 |
| cART naive | 0.69 | 0.13 - 3.56 | 0.656 |
| Pathology (DLBCL or Burkitt) | 1.36 | 0.30 - 6.11 | 0.686 |
| EBER positive in biopsy tissue sample | 0.94 | 0.13 - 6.67 | 0.950 |
| SUVmax of lesion in pretreatment PET ≥ 15 vs. < 15 | 1.64 | 0.10 - 26.35 | 0.726 |
| Interim PET/CT positive vs. negative | 4.57 | 0.88 - 23.73 | 0.070 |

OS: overall survival, HR: hazard ratio, ECOG: Eastern Cooperative Oncology Group, CNS: central nervous system, LDH: lactate dehydrogenase, cART: combination antiretroviral therapy, EBER: Epstein-Barr virus-encoded small RNA, DLBCL: diffuse large B cell lymphoma, SUV: standardized uptake value